

Dapsone is often tolerated in HIV-infected patients with history of sulfonamide antibiotic intolerance

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Clinical Implications

- Trimethoprim-sulfamethoxazole is the drug of choice for the prevention and treatment of *Pneumocystis jiroveci* pneumonia, but many patients have intolerance. Dapsone is the next best option, but contains sulfa moiety and cross-reactivity could occur. This study demonstrates that HIV patients with trimethoprim-sulfamethoxazole intolerance may tolerate dapsone.

TO THE EDITOR:

The drug of choice for the treatment and prevention of *Pneumocystis jiroveci* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX).¹ For patients who do not tolerate TMP-SMX, but require *Pneumocystis jiroveci* pneumonia prophylaxis, dapsone is the best next option compared with alternatives.¹⁻³ TMP-SMX and dapsone both contain a sulfa moiety and there is a theoretical concern for cross-reactivity, but they differ in that TMP-SMX is structurally a sulfonamide antibiotic and dapsone is a sulfone. Studies assessing cross-reactivity between sulfonamide antibiotics, specifically TMP-SMX, and dapsone are limited with conflicting results.⁴⁻⁸ Therefore, the aim of this study was to determine the likelihood of dapsone hypersensitivity in TMP-SMX-intolerant patients with HIV.

A retrospective chart review was performed using the local electronic medical record with institutional review board approval and consent was obtained from each patient. Patients with HIV were identified via *International Classification of Diseases, Ninth Revision* code. Only patients with a recent Minnesota address were included to try to ensure that documentation of medication exposure was accurate and comprehensive. Demographic data were captured for patients meeting these criteria. Patients were considered to have a sulfonamide antibiotic intolerance if any reaction to a sulfonamide antibiotic was listed in the allergy section of any clinical note and included in the study group compared with HIV patients without intolerance. Dapsone intolerance was further delineated in all patients with sulfonamide intolerance. Moreover, the outcomes of subsequent exposure to a sulfonamide antibiotic or dapsone and the location of the exposure (inpatient, outpatient, or both) were recorded.

A total of 1684 patients with an HIV *International Classification of Diseases, Ninth Revision* code had previously consented to chart review. Of these patients, 491 had a current mailing address in Minnesota. A total of 60 (12.2%) patients had a listed intolerance to sulfonamide antibiotics (sulfamethoxazole, sulfa, sulfonamides, Aczone, or Bactrim) and were included in the study group. In the study group, the mean age was 46.4 ± 15.1

years, 57.5% were white, and 72.6% were men versus the comparison group (n = 431) in which 66.7% were white and 80% were men with a mean age of 49.8 ± 9.58 years. Thirty-eight (63.3%) patients with sulfonamide antibiotic intolerance had other drug intolerances listed in the electronic medical record.

Patients with sulfonamide intolerance (n = 60) primarily suffered from cutaneous reactions (71.7%), but serious systemic reactions occurred in 10% (Table I). Six (10%) had reported intolerance to dapsone that manifested as cutaneous reactions (50%), but hematological reactions occurred in 2 (33%) patients (Table II). All but 1 of these patients had both intolerances before entry into the system. The only patient with more detailed reaction history had prior rash with TMP-SMX and experienced methemoglobinemia with dapsone secondary to incorrect dosing by the patient.

Repeat exposure to a sulfonamide occurred in 7 (11.7%) patients. Interestingly, 2 (28.5%) patients were prescribed TMP-SMX without a monitored or protocolized procedure and tolerated exposure. Three (42.8%) patients were exposed to TMP-SMX via either graded challenge (n = 1) and this patient reacted or had induction of tolerance via dose escalation without any adverse effect (n = 2). An additional 2 patients with previous intolerances to both TMP-SMX and dapsone attempted dose escalation to TMP-SMX. The first patient failed the dose escalation with recurrence of rash and the other patient succeeded but with difficulty requiring multiple redosing during escalation due to symptoms. Total success rate of TMP-SMX tolerance with repeat exposure was 71% (n = 5/7).

TABLE I. Reactions to sulfonamide antibiotics divided by category of reaction

Reactions to sulfonamide antibiotics	N
Serious systemic and cutaneous reactions	
Exfoliative dermatitis	1
Fever	1
Hepatitis	1
Pancytopenia	1
Rash with fever	1
Severe rash	1
Immediate-type hypersensitivity*	
Anaphylaxis	1
Angioedema with rash	1
Hives	7
Respiratory distress	2
Delayed-onset cutaneous reactions	
Rash	34
Other	
Unknown	4
Other	5

Delayed-onset cutaneous reactions were the most common (56.6%); serious systemic and cutaneous reactions were rare. Immediate-type hypersensitivities were documented, but also less common.

*Reactions were presumed to be <6 h if these specific categories were listed as the intolerance reaction.

TABLE II. Most HIV patients with TMP-SMX sensitivity tolerate dapsone, with rash being the most common reaction to TMP-SMX in both patients who did and did not tolerate dapsone exposure (N = 19)

Tolerated dapsone (N = 13 [68.4%])		
Bactrim reaction		Repeat SMX exposure
• Rash N = 7 (53.8%)		• N = 1 (7.7%)*
• Hives N = 1 (7.7%)		
• Exfoliative dermatitis N = 1 (7.7%)		
• Headache N = 2 (15.4%)		
• Unknown N = 2 (15.4%)		
Other drug sensitivities N = 7 (53.8%; <i>P</i> = .452)		
Dapsone intolerance (N = 6 [31.6%])		
Bactrim reaction	Dapsone reaction	Repeat SMX exposure
• Rash N = 6 (100%)	• Rash N = 3 (50%)†	• N = 2 (33.3%)
	• Hemolytic anemia N = 1 (16.6%)‡	
	• Drug fever N = 1 (16.6%)	
	• Methemoglobinemia N = 1 (16.7%)§	
Other drug sensitivities N = 5 (83.3%; <i>P</i> = .452)		

Repeat exposure to TMP-SMX was rarely performed (15.8%) and with difficulty.

*Patient developed rash to TMP-SMX exposure in typical fashion after dapsone was tolerated.

†One of the patients was exposed to TMP-SMX and dapsone concurrently, with rash listed as intolerance to both medications without further evaluation. The patient was later desensitized to TMP-SMX with difficulty.

‡Patient was not evaluated for glucose-6-phosphate-dehydrogenase deficiency.

§Patient underwent induction of tolerance to TMP-SMX with difficulty.

||Both patients underwent TMP-SMX dose escalation. The first patient failed dose escalation because of recurrence of rash similar to initial reaction toward TMP-SMX. The second patient completed dose escalation, but required multiple repeat doses and treatment of symptoms.

Thirteen (21.7%) patients received dapsone and all these patients tolerated dapsone (Table II). Dapsone was used in the inpatient setting (30.8%), in the outpatient setting (30.8%), and in both settings (38.4%). The initial intolerance reactions to TMP-SMX are listed in Table II and involved cutaneous reactions in 9 (69.2%) patients. It is important to note that 1 of the patients had exfoliative dermatitis to TMP-SMX and still tolerated dapsone. These 13 patients commonly (53.8%) had other drug intolerances at a frequency not significantly different than that from patients with sulfonamide and dapsone intolerance (83.3%; *P* = .452) (Table II).

TMP-SMX (sulfonamide) and dapsone (sulfone) contain a sulfa moiety, but differ by structure and activity. Likelihood of cross-reactivity between sulfonamide antibiotics and sulfones is not well known. Our study demonstrates tolerance to dapsone in patients with a history of TMP-SMX intolerance. However, 10% of the patients with TMP-SMX intolerance also reported a history of dapsone intolerance before entry into the health system, suggesting possible cross-reactivity. In contrast, cross-reactivity between TMP-SMX and dapsone in HIV patients has been reported to be quite common.^{5,7,8} However, consistent with our study, other studies have shown lower cross-reactivity rates (12%-17%).^{4,6} Our study adds to literature demonstrating that HIV patients with a history of TMP-SMX intolerance may tolerate dapsone. This tolerance of dapsone may be related to low cross-reactivity, but also might be due to partial or complete loss of sensitivity to sulfonamide antibiotics with time. This may also be the reason for variation in reported cross-reactivity rates in the literature.⁴⁻⁸

Interestingly, in our study, only 12.2% of HIV patients had documented sulfonamide intolerance, which is significantly lower than that reported in previous studies (over 80%).² However, the incidence in this study is similar to the incidence of cutaneous reactions documented by Coopman et al⁹ at 8.1% and most of our reactions were cutaneous (71.7%). The reason for such a discrepancy could be related to study design and missed intolerances due to lacking documentation. Another factor could be related to the population seen at our institution. CD4 count was not considered in the inclusion criteria. Therefore, perhaps most of these patients have a higher CD4 count, limiting exposure to TMP-SMX. This is important because CD4 count at the time of exposure to the medication seems to alter the risk of developing intolerance toward TMP-SMX.⁶

In patients with sulfonamide intolerance, repeat TMP-SMX exposure occurred in 7 (11.7%) patients. Overall, reexposure was successful via challenge or dose escalation in 71% of these patients including 2 patients who were given TMP-SMX in typical fashion without any adverse event. However, intolerance to both TMP-SMX and dapsone may lead to difficulty tolerating TMP-SMX. Two patients met these criteria and 1 (50%) failed and the other patient had difficulty with dose escalation.

In this study, none of the 13 patients with a history of sulfonamide intolerance exposed to dapsone had an adverse drug reaction. Therefore, a dapsone trial could be considered in HIV patients with a history of TMP-SMX intolerance. However, patients with severe drug hypersensitivity reactions to TMP-SMX should continue to avoid dapsone.

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This study was approved by the Mayo Clinic Institutional Review Board as a low-risk study.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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